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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,789	06/12/2000	John J. Machalonis	7760-012	5233

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/591,789	MACHALONIS ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ ~~Notice of References Cited (PTO-892)~~

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12052003; 01242003*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 05 December, 2003, has been entered.

Status of the Claims

Claims 7, 24, and 25 are currently under examination.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 24, and 25 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward a method for increasing T_H1 cytokine production while decreasing T_H2 cytokine production through the administration of a peptide comprising SEQ ID NO.: 1. The purpose of this modulation is to

prevent and/or treat cardiovascular disease, allergic disorders, solid tumors, and the progression to AIDS in an HIV-positive patient (see specification, first paragraph, p.1). The invention appears to be predicated upon the assumption that these various pathologies can be treated by shifting the immune state of a patient from that of a T_H2 state, which is generally associated with phagocyte-independent immune responses (i.e., IgE production, IgG production, mast cell activation and differentiation), to one of a T_H1 state, which is generally associated with phagocyte-dependent immune responses (i.e., delayed-type hypersensitivity, production of opsonizing antibodies, production of complement-fixing antibodies).

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure still fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating the favorable immunological properties and activities of the claimed peptide. The claimed invention involves the administration of a T-cell receptor (TCR) peptide to the patient. The TCR is a heterodimeric cell surface protein comprising an α and β polypeptide that is normally involved

in a number of immunological responses such as antigen recognition (Davis and Chien, 1999). The TCR recognizes antigenic peptides presented in the context of MHC class I or II. Each α and β subunit is glycosylated and has a molecular weight of 40,000-50,000. TCRs are quite diverse and share structural similarities with immunoglobulins including variable, constant, and joining regions. Thus, they are quite complex molecules. **Although it is noted that this peptide is derived from the first CDR TCR Vβ domain, it is not readily manifest how the administration of this peptide will modulate the immune response in favor of T_H1-type responses. The disclosure fails to provide any guidance pertaining to the biochemical and immunological activities of the claimed peptide (i.e., agonist or antagonist). For instance, does the peptide act by inhibiting TCR interactions on $CD4^+$ T-lymphocytes or does it function in some other manner. How will the skilled artisan keep the peptide from interfering with normal TCR interactions on both $CD4^+$ and $CD8^+$ T-lymphocytes? What will preclude the patient from developing an immune response against the peptide of interest thereby leading to aberrant immunological activity (i.e., down-modulation of TCR-mediated immune responses)?** These are reasonable immunological concerns that are simply not addressed by the specificaiton.

Applicants traverse and argue that the TCR peptide employed in the claimed methodology is described in U.S. Patent No. 5,911,990. This teaching discloses that the peptide of interest corresponds to the first CDR region of the T-cell receptor Vβ domain. The origins of this peptide have been noted. However, the '990 patent fails to address any of the aforementioned immunological concerns. The disclosure of the '990 patent was directed toward a murine immunodeficiency model which bears little or no resemblance to the states being modulated in the existing application. Thus, any

findings in that application cannot be directly extrapolated to the instant application.

Applicants also submitted that there this no legal requirement that a knowledge of the underlying mechanism of action be understood. While there is no explicit legal requirement that the mechanism of action be partially or completely understood, nevertheless, in claims that are extremely broad and encompass numerous species (i.e., any derivative of SEQ ID NO.: 1) or are directed toward arts that are extremely unpredictable (i.e., the of immunotherapeutic strategies to treat cancer, cardiovascular disorders, and infectious diseases) the identification of such information would help the skilled artisan make a reasonable determination as to whether or not the claimed invention would be expected to function in the manner claimed. In this particular application, the absence of a better understanding of the mechanisms underlying the therapeutic properties of the peptides of interest are certainly a short-coming. For instance, the skilled artisan cannot reasonably predict which peptidic derivatives will have the desired properties since the specification fails to provide any guidance pertaining to the molecular determinants modulating these activities.

Moreover, the Examiner raised a number of legitimate scientific issues that were ignored in the response. For instance, the following items were raised: (i) it is not readily manifest how the administration of this peptide will modulate the immune response in favor of T_H1-type responses; (ii) the disclosure fails to provide any guidance pertaining to the biochemical and immunological activities of the claimed peptide (i.e., agonist or antagonist); (iii) it is not readily manifest how the skilled artisan will keep the peptide of interest from interfering with normal TCR interactions on both $CD4^+$ and $CD8^+$ T-lymphocytes; (iv) it is not readily manifest what will preclude the patient from developing an

immune response against the peptide of interest thereby leading to aberrant immunological activity (i.e., down-modulation of TCR-mediated immune responses). None of these concerns were adequately addressed in the reply.

2) The disclosure fails to teach that modulating T_H1/T_H2 cytokine levels will have any ameliorative or therapeutic effect in cardiovascular disease, allergic disorders, or solid tumors. The correlates of protective immunity for many disorders remain to be elucidated. Moreover, **many pathogens and disease states fail to elicit a simple T_H1 or T_H2 phenotype** (Graziosi *et al.*, 1994; Maggi *et al.*, 1994; Romagnani *et al.*, 1994; Shearer and Clerici, 1992). For instance, **it is not clear what type of immune responses will protect against solid tumors, allergic disorders, cardiovascular disease**, or the progression to AIDS. In some situations, both humoral and cell-mediated immune responses may be required. Thus, the interplay between "T_H1/T_H2" cytokine responses may not be so simple. In fact, what is more likely to required, is a balance between the two responses to favorably eliminate tumors and HIV. It is not readily manifest how the peptide of interest would facilitate the treatment of cardiovascular disease. For instance, would the peptide be capable of inducing immune responses that remove plaque from clogged arteries? What type of allergic disorders could the peptide of interest prevent or treat? Absent sufficient guidance from the disclosure, the skilled artisan has been extended an undue invitation to further experimentation.

Applicants traverse and submit that there is no requirement that any of these disease states be treated. Applicants argue that all that is required is to simply increase production of at least one T_h1 cytokine or decrease production of a T_h2 cytokine. Applicants arguments' are specious at best. What is the purpose of altering the T_h1/T_h2 cytokine profile? The whole purpose of modulating these profiles is to treat an underlying pathology. Simply altering the

cytokine profile without having any other measurable effect would lead the skilled artisan to question the utility and use of such an invention. However, it is readily manifest from reading the disclosure that the purpose of this modulation is to clearly treat an autoimmune pathology. Accordingly, the breadth of the claims certainly encompasses these applications and the disclosure must be enabling for said applications. However, as set forth in this rejection, the disclosure clearly fails to enable the claimed invention.

Applicants previously argued that the issues raised by the Examiner are directed toward a lack of utility and should be addressed under the Utility Guidelines (M.P.E.P. § 2107). Applicants note that all that is required under these guidelines is that a "reasonable" correlation between the effectiveness of the methods and asserted use be provided. These arguments are completely misdirected. The crux of this aspect of the rejection is clearly directed toward the ability of a TCR peptide to modulate T_H1/T_H2 cytokine levels in such a manner that it can reasonably be expected to have some sort of ameliorative or therapeutic effect in cardiovascular disease, allergic disorders, solid tumors, or the progression to AIDS. Applicants are reminded that the present rejection is based solely upon those tenets governing 35 U.S.C. § 112, first paragraph, rejections. This is not a rejection based upon 35 U.S.C. § 101. Rejections made under 35 U.S.C. § 112, first paragraph, address different issues from those examined under the utility guidelines. These issues include whether the claims are fully supported by the disclosure (*In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991)), whether the applicant has provided an enabling disclosure of the claimed subject matter (*In re Wright*, 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)), and whether the applicant has provided an adequate written description of the invention (*Chemcast Corp. v.*

Arco Industries Corp., 913 F.2d 923, 927-928, 16 U.S.P.Q.2d 1033, 1036-1037 (Fed. Cir. 1990)). The preceding paragraph raised a number of legitimate scientific concerns which were ignored in the response. Applicants are invited to provide any data or publications that suggest that the administration of a TCR peptide can reasonably be expected to protect against solid tumors, allergic disorders, cardiovascular disease, or the progression to AIDS.

3) The disclosure fails to provide any working embodiments. The disclosure fails to provide any relevant models of tumor progression, cardiovascular disease, or allergic disorders. The disclosure fails to provide any data involving the claimed peptide demonstrating that it can effectively treat tumor development, cardiovascular disease, or sundry allergic disorders. The development of any given therapeutic is a difficult process involving testing of the peptide or compound of interest in *in vitro* tissue culture assays, *in vivo* animal models, and finally in preliminary clinical studies. Only be performing such studies can the skilled artisan reasonably conclude that such compounds will be efficacious (Öberg and Vrang, 1990; Gait and Karn, 1995; Yarchoan and Broder, 1992). However, the disclosure fails to provide suitable evidence in support of the claimed activity of the TCR peptide.

Applicants again reference the '990 patent and again suggest that the MAIDS model described therein is a reasonably model for tumor progression, cardiovascular disease, and allergic disorders. Contrary to applicants' assertions, this model is not representative of these human disorders. Moreover, the findings of the MAIDS model cannot be directly extrapolated to human systems due to the various genetic and pathological differences. Applicants also previously argued that there is no legal requirement that working embodiments be provided. Once again,

while there may be no explicit requirement for such embodiments, nevertheless, in complex biotechnology applications, such as the instant one, the inclusion of working embodiments would facilitate the determination of enablement under 35 U.S.C. § 112, first paragraph. The failure to have any working embodiments suggests that Applicants have not been able to demonstrate that the claimed invention functions as claimed. Applicants are also directed to *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986), wherein the courts clearly noted that the presence or absence of working examples was an important consideration in making enablement determinations under this statute. Applicants are invited to provide any data demonstrating that the claimed TCR peptide, or derivatives thereof, were capable of modulating immune response in the desired manner.

4) As discussed *supra*, the prior art is unpredictable and teaches that the development of efficacious treatments for cardiovascular disease, allergic disorders, and solid tumors, is an arduous and often unsuccessful undertaking (Graziosi *et al.*, 1994; Maggi *et al.*, 1994; Romagnani *et al.*, 1994; Shearer and Clerici, 1992; Öberg and Vrang, 1990; Gait and Karn, 1995; Yarchoan and Broder, 1992). **Moreover, the complexity of the TCR and the various roles it plays in T-cell signaling make it difficult to identify and predict which compounds will prove useful as therapeutic agents** (Evavold *et al.*, 1993; Madrenas *et al.*, 1996). Perusal of the disclosure fails to provide any evidence that would lead the skilled artisan to conclude otherwise. Applicants' response failed to address this concern and provide any objective scientific evidence addressing these concerns.

5) The claims are of considerable breadth and remain unsupported by the disclosure. The claims encompass the treatment of any solid tumor, any cardiovascular disorder, and any allergic disorder, employing the claimed TCR receptor peptide. As noted above, the

disclosure fails to provide support for any of these claims. The first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Clearly the inventors have not met their obligation under this section.

Applicants appear to contend once again that the issues raised by the Examiner are directed toward a lack of utility and should be addressed under the Utility Guidelines (M.P.E.P. § 2107). Once again this argument is completely misdirected. The crux of this aspect of the rejection is clearly directed toward the breadth of the claimed invention. Applicants are attempting to modulate T_H1/T_H2 cytokine responses through the administration of a TCR peptide, or derivative thereof, in such a manner that it can reasonably be expected to have some sort of ameliorative or therapeutic effect in cardiovascular disease, allergic disorders, solid tumors, or the progression to AIDS. Apparently Applicants' representative does not understand or appreciate the breadth of the claimed invention. These four areas encompass a large number of complex and diverse disorders. Many of these pathologies involve fundamentally different, but complex, mechanisms of action. Moreover, the claims encompass the administration of a large genus of TCR peptide derivatives whose properties are completely unknown. Applicants are again reminded that the present rejection is based solely upon those tenets governing 35 U.S.C. § 112, first paragraph, rejections. This is not a rejection based upon 35 U.S.C. § 101. Rejections made under 35 U.S.C. § 112, first paragraph, address different issues from those examined under the utility guidelines. These issues include whether the claims are fully supported by the disclosure (*In re Vaeck*, 947 F.2d 488, 495,

20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991)), whether the applicant has provided an enabling disclosure of the claimed subject matter (*In re Wright*, 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)), and whether the applicant has provided an adequate written description of the invention (*Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923, 927-928, 16 U.S.P.Q.2d 1033, 1036-1037 (Fed. Cir. 1990)).

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the claimed invention.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (571) 272-1600.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

21 March, 2004